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High Frequency Heart Rate Variability During Worry Predicts Stress-Related Increases in Sleep Disturbances

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Highlights

- HF-HRV (high-frequency heart rate variability) was related to sleep quality.
- HF-HRV during low stress was related to sleep quality during high stress.
- HF-HRV reactivity to worry prospectively predicted stress-induced sleep disturbances.

Abstract

Objective: Evaluate whether high frequency heart rate variability (HF-HRV) during waking restfulness and during worry predicts increases in sleep disturbances in response to a stressful life event.

Methods: Longitudinal study following 22 individuals from well-defined periods of lower and higher stress. HF-HRV during waking restfulness and in response to a worry induction were measured during a low stress period. Sleep disturbances were assessed using the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI) during low stress and high stress periods.

Results: During both the low and high stress periods, lower HF-HRV during worry was associated with greater PSQI scores. Importantly, lower HF-HRV during the worry induction prospectively predicted greater increases in the PSQI score from the low stress to the high stress periods.

Conclusion: HF-HRV during worry might represent an index of vulnerability to stress-induced sleep disturbances.

Keywords: Heart rate variability; autonomic function; insomnia; stress; worry.

1. Introduction

Contemporary models of insomnia suggest that stress is a common precipitating factor triggering the onset of insomnia episodes.[1-4] In both cross-sectional and longitudinal studies, a greater number of stressful life events have been associated with increased risk for experiencing insomnia symptoms and syndrome.[5-12] However, while there is a significant relationship between stress exposure and increases in insomnia symptoms, most people who experience stressful life events do not develop persistent sleep disturbances.[13]

There are documented individual differences in vulnerability to stress-induced sleep disturbances.[14] Bonnet & Arand[15] observed that some individuals experienced sleep disturbances across different situations involving change in their sleep environment or habits, such as during the first night in a sleep laboratory, during a phase advance of sleep time by 3 or 6 hours, or after caffeine consumption, while other individuals did not exhibit sleep reactivity in response to any of these manipulations. Furthermore, individuals who had a higher score on the Ford Insomnia Response to Stress Test (FIRST),[16] a self-reported measure of vulnerability to stress-induced insomnia, had a more pronounced first night effect, that is lower sleep efficiency during the first night at the sleep laboratory, and greater sleep disturbances following caffeine administration close to bedtime than participants with less vulnerability to stress-induced sleep disturbances.[16,17] In longitudinal studies, higher FIRST scores were associated with increased risk of developing insomnia symptoms, syndrome, or persistent insomnia over time, highlighting the impact of individual differences in sleep reactivity to stress.[12,18]

Physiological and emotional arousal are thought to contribute to the development of sleep disturbances in response to stress.[19] High frequency heart rate variability (HF-HRV), an index of autonomic activity analogue to respiratory sinus arrhythmia, represents the oscillations in inter-beat intervals during the respiration cycle.[22] Pharmacological blockade studies indicate that HF-HRV is modulated by vagal-dependent cholinergic neurotransmission at the sinoatrial node of the heart and indexes parasympathetic activity.[22] Furthermore, the brainstem nuclei regulating HF-HRV are sites of integration of afferent ascending projections of the vagal nerve as well as efferent projections from the central autonomic network, and, indirectly, from the amygdala and prefrontal cortex.[20,21] As such, HF-HRV has been conceptualized as a marker of physiological and emotional arousal regulation.[20,21]

Lower HF-HRV during waking restfulness was associated with larger and longer lasting elevations in heart rate, diastolic blood pressure, cortisol, and tumor necrosis factor-α in response to emotional stressors[23-26] and greater startle response to unpleasant stimuli.[27,28] Lower HF-HRV during waking restfulness has also been associated with greater anxiety and depression responses to stress in cross-sectional,[29-32] experimental,[34] and prospective studies.[37] Furthermore, HF-HRV decreases in response to emotional stressors[38]. HF-HRV reactivity to emotional stressors was related to concurrent and prospective emotional responses to stress, independent of resting HF-HRV.[38-43]

HF-HRV during waking restfulness has been related to sleep quality. Bonnet and Arand[15] found that individuals who displayed situational insomnia across a range of circumstances had lower HF-HRV to total spectral power ratio during morning wakefulness, compared to individuals who

did not experience these stress-induced sleep disturbances. Furthermore, among individuals with panic disorder and depression, lower HF-HRV was related to greater self-reported sleep disturbances.[44-46] In children, lower HF-HRV during waking restfulness was associated with worse actigraphy-derived sleep efficiency.[47] Furthermore. HF-HRV reactivity to stressor was related to self-reported sleep quality in depressed and non-depressed individuals[45] and was associated with worse actigraphy-derived sleep efficiency and prolonged wake episodes after sleep onset among children[48,49] and adult women with breast cancer[50], independent of resting HF-HRV.

Collectively, these results indicate that HF-HRV during waking restfulness and HF-HRV reactivity to emotional stressors are related to sleep quality in healthy and clinical populations. However, given the cross-sectional nature of these studies, the directionality of this relationship cannot be teased apart. That is, it is unclear whether lower HF-HRV is a consequence or a predictor of poor sleep in response to stress.[51] This is a crucial issue given that HF-HRV decreases following sleep deprivation.[52-54] Longitudinal studies are thus needed to examine whether HF-HRV during a period of lower stress predicts vulnerability to sleep disturbances during periods of higher stress.

The goal of the present study was to prospectively evaluate whether HF-HRV during waking restfulness and HF-HRV in response to an emotional stressor would predict the development or exacerbation of sleep disturbances in response to stress. To examine this question, we evaluated changes in sleep disturbances in response to a naturalistic stressor among a population of university students comprising both good sleepers and individuals with insomnia symptoms.

Academic stressors are characterized by well-defined periods of lower stress at the beginning of the semester followed by higher stress starting during the week prior to the final examinations.[55] Both perceived stress and sleep disturbances increase from the low stress to the high stress periods,[56,57] providing an excellent opportunity to examine individual differences in changes in sleep quality in response to a naturalistic, yet fairly standardized stressor. A worry induction paradigm, eliciting personally relevant worries, was used to assess HF-HRV reactivity to an emotional stressor during the low stress period.[55] We hypothesized that lower HF-HRV during both resting wakefulness and in response to a worry induction would prospectively predict larger increases in sleep disturbances in response to stress.

2. Materials and Methods

Prospective participants completed screening questionnaires (FIRST[16]) and an overnight polysomnography (PSG) to assess eligibility. Eligible participants completed the HF-HRV testing during the low stress period, i.e., within the first 4 weeks of a 15-week academic semester. Furthermore, participants completed self-report assessments of sleep disturbances (ISI, PSQI) during the low stress and the high stress (i.e., during the week prior to the final examination) periods. Figure 1 depicts the study assessment schedule.

Insert Figure 1 about here

2.1. Participants

Participants were recruited through advertisements among undergraduate students in Psychology or Exercise Science at Concordia University. During the screening procedure, participants completed the FIRST questionnaire. To ensure a wide range of range of vulnerability to stress-related sleep disturbances within the sample, participants with FIRST scores above 24 or below 16 were oversampled, and an equal number of participants above and below 20 were selected. These values of 24 and 16 represent one standard deviation above and below the mean FIRST score of 20 in a large study of 1782 individuals.[59] Participants also completed the Epworth Sleepiness Scale[58] an overnight PSG to screen out individuals with sleep disorders other than insomnia (e.g., sleep apnea). Other exclusion criteria included any chronic medical conditions, regular medication use (including any hypnotic medication), a history of head trauma, smoking, current shift work, and age greater than 30. Both good sleepers and individuals with insomnia symptoms were included in the study given the findings that stress leads to the development, as

well as the maintenance and exacerbation of sleep disturbances.[5,9,18] All participants provided informed consent prior to participation in the study, which was approved by the local Human Research Ethics Committee.

2.2. Questionnaires

The **Ford Insomnia Response to Stress Test (FIRST)** is a 9-item self-report questionnaire assessing vulnerability to sleep reactivity to stress.[16] This questionnaire was administered once during the screening session. The **Insomnia Severity Index (ISI)** is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia symptoms within the past 2 weeks.[60] The **Pittsburgh Sleep Quality Index (PSQI)** is a 19-item self-report measure assessing subjective sleep quality in the past month.[61] These last two questionnaires were completed twice, during the low and high stress period.

2.3. Polysomnography (PSG)

PSG consisted of a 34-channel system with EEG referenced to linked-mastoids (bandpass filter 0.3-100 Hz, sampling rate 256 Hz), electrooculography (EOG), electromyography (EMG; submental, tibial), nasal-oral thermocouple airflow, and transcutaneous finger pulse oximeter. Sleep was recorded and scored according to standard methods.[63] No periodic leg movements during sleep were observed. Exclusion criteria included an apnea-hypopnea index > 5. No participant met this exclusion criterion.

2.4. HF-HRV measurement

At the beginning of the testing session, participants were fitted with a chest belt hardwired with a digital inter-beat interval recorder (Polar RS800CX; Finland: Kempele). For the waking restfulness baseline, participants were instructed to close their eyes and relax as much as possible for 5 minutes. After the resting baseline, the participants completed a 3-minute worry induction task. Based on the Hoffman et al. [64] protocol, participants were presented with a definition of worry ("a chain of negative thoughts about something that can have negative consequences in the future"), asked to identify the topic they tend to worry the most often and most intensely about, and to worry about this topic for the next 3 minutes. Participants remained seated and were asked to breathe normally throughout the resting baseline and worry induction task. HF-HRV measurements were collected once, during the low stress period only. The laboratory session was scheduled between 8:00 to 9:00 PM to minimize the impact of diurnal variations in HF-HRV.[65] Participants were asked to refrain from exercising and drinking caffeinated beverages at least 8 hours prior to the laboratory session.[22]

The telemetric inter-beat interval recording device recorded the interval between successive R-spikes of consecutives QRS complexes using a sampling rate of 1000 samples per second throughout the testing session. Recording artifacts were identified and corrected using the CardioEdit software.[66] Artifact correction was performed using integer arithmetic (i.e., dividing or adding intervals between heartbeats to correct missed or spurious R-spike detections). Less than 1% of the beats were edited for each participant. Porges and Bohrer's[67] moving polynomial approach was used to extract HF-HRV using the CardioBatch software.[68] A moving polynomial filter was applied to heart rate time series to remove the influence of aperiodic processes and to

generate a detrendred residualized time series. A bandpass filter was applied to the detrended time series to extract the variance associated with oscillations in the interbeat intervals across the respiration cycle (.12-.40 Hz). The average HF-HRV across each sequential 30-second epoch within each condition was calculated to minimize the impact of violation of the stationarity assumption. The HF-HRV metric is the natural logarithm of the variance of the bandpassed time series. This method provided an optimal assessment of vagally-mediated cardiac activity.[69] Averaged HF-HRV was calculated for the two testing phases: waking restfulness and the worry induction.

2.5. Statistical analysis

Pearson correlation evaluated bivariate correlations among the main study variables (i.e., FIRST, HF-HRV, ISI, PSQI). General linear model repeated measures analysis evaluated the change over time in self-reported sleep disturbances (ISI, PSQI) from the low stress to the high stress period. Changes in ISI and PSQI over the time were the within-subject factors. The HF-HRV variables during the low stress period were the between-subject factors. Sex and field of study were also included as covariates. All analyses were conducted with SPSS 20.0.

3. Results

Participants (N=22) were full-time undergraduate students. About 77.3% of participants were females. Reflecting the ethnic diversity of our institution, 52.17% were Caucasians, 17.39% were Native Americans, 13.04% were Latinos, 8.69% were Asians, 4.35% were Blacks, and 26.09% identified as Biracials. About 60% of the participants were Psychology majors; the remainders were Exercise Science majors.

Descriptive statistics, including demographics, PSG parameters, questionnaires and HF-HRV variables, are presented in Table 1. At baseline, 36% of the sample had an ISI score of 10 or above, indicating possible clinical insomnia. For the PSQI, 54% of the participants had a score of 5 and above, suggestive of poor sleep. Table 2 presents the bivariate relationships between the FIRST score, HF-HRV during rest and worry, and indices of self-reported sleep quality at the low and high stress periods. Notably, there was a significant negative relationship between the FIRST score and HF-HRV during worry.

3.1. Changes in self-reported sleep quality from the low stress to the high stress period.

There was no significant change in ISI score from the low to the high stress periods, $F(1,19) = 1.46$, $p = .25$, $\eta^2 = .07$. Similarly, there was no significant increase in PSQI score from the low to the high stress periods, $F(1,19) = 1.42$, $p = .25$, $\eta^2 = .07$.

3.2. Changes in self-reported sleep quality as a function of self-reported vulnerability to stress-induced insomnia

Bivariate relationships indicated that the FIRST score was significantly correlated with both the ISI and the PSQI at the low- and high- stress assessments (Table 2). However, baseline FIRST score did not significantly predict the change in the ISI, $F(1,18) = 1.23$, $p = .28$, $\eta^2 = .06$, or in the PSQI, $F(1,18) = 1.60$, $p = .22$, $\eta^2 = .08$, over time.

3.3. Changes in self-reported sleep quality as a function of HF-HRV

Bivariate correlations indicate that HF-HRV during waking restfulness was marginally associated with PSQI score during the low stress period and significantly associated with the PSQI during the high stress period (Table 2). In contrast, resting HF-HRV was not associated with ISI scores at either time point. Furthermore, HF-HRV during waking restfulness was not significantly associated with changes in the ISI, $F(1,18) = .87$, $p = .36$, $\eta^2 = .05$, or the PSQI, $F(1,18) = 2.28$, $p = .15$, $\eta^2 = .11$, over time.

There was a significant reduction in HF-HRV from the resting baseline to the worry induction, $F(1,22) = 11.45$, $p = .003$, $\eta^2 = .34$. HF-HRV during worry was significantly correlated with PSQI scores during both the low and high stress periods (Table 2). Similarly, HF-HRV during worry was marginally associated with ISI scores during the low stress period, but significantly associated with ISI scores during the high stress period. Although HF-HRV during the worry induction did not predict change in ISI over time, $F(1,18) = 1.07$, $p = .31$, $\eta^2 = .06$, it significantly predicted changes in PSQI from the low stress to the high stress period, $F(1,18) = 5.84$, $p = .03$, $\eta^2 = .25$. Results indicated that lower HF-HRV during worry was associated with larger stress-related increases in sleep disturbances as assessed by PSQI. Figure 2 depicts the relationship between HF-HRV during worry and stress-related increases in the PSQI score.

Insert Figure 2 about here

3.4 Secondary analysis of the individual ISI items and PSQI components.

Secondary analyses were conducted to examine whether HF-HRV predicted changes in individual ISI items or PSQI components. HF-HRV did not predict any of the insomnia symptoms items, all $p > .40$. However, HF-HRV during worry predicted increases in worry and distress about current sleep problems, $F(1,18) = 4.68$, $p = .04$, $\eta^2 = .21$, such that individuals with lower HRV during worry had greater increases in worry and distress regarding their current sleep problems than participants with higher HF-HRV. For the PSQI components, HF-HRV during worry only significantly predicted changes in daytime dysfunction component of the scale, $F(1,18) = 8.81$, $p = .01$, $\eta^2 = .33$, such that individuals with lower HRV-HRV during worry reported greater increases in sleep-related daytime dysfunction from the low stress to the high stress period.

4. Discussion

The goal of this study was to examine whether low HF-HRV is a risk factor for stress-related increases in sleep disturbances. HF-HRV during worry was associated with sleep quality, as assessed by the PSQI, during both the low stress and high stress periods. Importantly, lower HF-HRV during worry predicted greater increases in sleep disturbances from the low stress to the high stress periods. The prospective nature of these analyses indicates that lower HF-HRV during worry is not only a mere consequence of poor sleep, but also an independent predictor of increases in sleep disturbances in responses to stress.

Contemporary theories suggest that increased physiological and emotional arousal interfere with sleep onset and maintenance.[19] Stress induces elevations in a number of markers of physiological arousal, such catecholamine, glucocorticoid, and inflammatory markers that are known to disrupt sleep.[70] Converging lines of evidence indicate that individuals with low HF-HRV exhibit more pronounced and sustained elevations in these markers of physiological arousal in response to stress, rendering them more vulnerable to sleep disturbances.[23,24,37] Furthermore, individuals exhibiting more sleep reactivity to stress may have dysregulated diurnal and nocturnal autonomic activity.[15] During sleep, there is an increase in HF-HRV across NREM sleep cycles and a reduction during REM sleep.[71] During NREM sleep, HF-HRV covaries with delta EEG power, highlighting the interconnection between autonomic changes and sleep physiology.[72] In an ambulatory study, individuals who experienced more worry in response to stress had lower HRV during the worry period, but also during the following night,[73] suggesting that diurnal worry-related changes in HRV might impact nocturnal autonomic activity and sleep quality. Moreover, lower HF-HRV has also been associated with greater emotional arousal in response to stress.[21]

Poorer emotion regulation during stressful times is often translated into higher emotional and cognitive arousal at bedtime, which, in turn, is related to poorer sleep.[74,75] Impaired physiological, emotional, and cognitive arousal regulation thus represents potential pathways through which low HF-HRV might increase vulnerability to stress-related sleep disturbances.

Prior studies indicate that both resting HF-HRV and HF-HRV reactivity to emotional stressors independently predict sleep quality.[48] In the present study, there was a significant decrease in HF-HRV during the worry induction[76-78] and HF-HRV during worry was more strongly associated with sleep disturbances than HF-HRV during resting wakefulness. Porges (2007) argues that vagal withdrawal, indicated by HF-HRV suppression, facilitates energy mobilization in responses to stress. However, vagal withdrawal to worry, an emotional stressor associated with no actual physical threat, may indicate increased emotional and physiological reactivity to stress. Indeed, decreased HF-HRV during worry prospectively predicted greater negative emotional responses to stress.[38] HF-HRV during worry might thus provide a unique index of vulnerability for stress-induced sleep disturbances.

Given the well-defined nature of academic stressors, this paradigm represents an ideal situation to examine inter-individual variability in vulnerability to stress-induced sleep disturbances. To further enhance the likelihood of observing these individual differences, individuals with high and low self-reported risk for stress-induced insomnia were oversampled. Although there was no overall change in sleep disturbances from the low stress to the high stress periods, HF-HRV during worry identified the portion of participants who did experience stress-induced worsening of self-reported sleep quality. Surprisingly, despite a significant correlation between the FIRST

score and HF-HRV during worry, the FIRST score did not predict stress-related changes in sleep disturbances. This might be explained by the large correlations between the FIRST score and indices of self-reported sleep quality at baseline in this sample (e.g. $r_{FIRST-ISI} = .79$), leaving little room to predict change over time.

HF-HRV was associated with both the ISI and PSQI during the high stress period, providing further evidence for the inter-relationship between sleep and parasympathetic activity. However, HF-HRV during worry predicted changes in sleep quality as assessed by the PSQI, but not change in insomnia symptoms, as assessed by the ISI. While the ISI focuses on insomnia symptoms and their consequences, the PSQI also assesses sleep duration, sleep efficiency, as well as a range of factors associated with sleep disturbances over a longer timeframe. Secondary analyses indicated that HF-HRV during worry predicted changes in the worry about sleep problems of the ISI and the poor sleep-related daytime dysfunction component of the PSQI. This is in line with the conceptualization of the HRV as a marker of emotion regulation to stress[21]. This raises the possibility that lower HF-HRV during worry might also impact one's ability to efficiently cope with poor sleep and foster the adoption of counterproductive behavior and cognition in order to cope with sleep loss. As such, differences in the assessment of daytime dysfunction and distress might explain why HF-HRV during worry predicted the PSQI and not the ISI.

A limitation of the current study was the fact that it included only university students. This was necessary given the need to identify a well-defined and fairly standardized stressor across participants. Moreover, academic examinations are predictable, time-limited stressors occurring

over several consecutive days. Some studies indicate that HF-HRV predict greater responses to unpredictable rather than predictable stressors.[79] Future studies should examine whether HF-HRV during worry predicts the onset or exacerbation of sleep disturbances to unpredictable, recurrent, or chronic stressors. Furthermore, future studies should include longer follow-ups to examine whether HF-HRV during worry predicts not only the onset or exacerbation, but also the persistence of stress-related sleep disturbances over time in both community and clinical samples. Although we hypothesize that HF-HRV would predict physiological and emotional arousal in response to stress, these potential mediators were not measured explicitly. Finally, sleep outcome measured in the current study were limited to self-reported subjective questionnaires. PSG data were only collected at baseline (during the low stress period) for screening purposes. Indeed, the very nature of the stressor (academic examinations) precluded the repetition of the PSG during the high stress period, since participants would most likely not be willing to undergo an overnight sleep recording in the laboratory at that time. Future studies might use other types of stressors more compatible with repeated PSG, or might alternatively resort to more practical objective measures of sleep such as actigraphy measurements.

5. Conclusion

In summary, this study provides further evidence of the inter-relationship between parasympathetic functioning and sleep. HF-HRV during worry prospectively predicted stress-related worsening in sleep quality. As such, HF-HRV in response to an emotional stressor might represent a marker of physiological and emotional arousal regulation that predicts vulnerability to stress-induced sleep disturbances. Future studies should explore the potential clinical utility of this biomarker.

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Figure 1. Study Assessment Schedule.

Figure 2- Changes in self-reported sleep quality (PSQI) from the low stress to the high stress period as a function of baseline HF-HRV during worry. For illustration purposes, the continuous HRV during worry values were dichotomized into low and high HRV values using a median split. Error bars represent standard errors of the means.

Table 1. Demographic, psychological, polysomnographic, heart rate variability, and subjective sleep characteristics of the study participants.

	M (SD)	*Range*
Age	21.31 (2.14)	19-25

Table 2. Pearson's inter-correlations among the main study variables.

FIRST	21.91 (7.10)	11-32
ESS	7.35 (3.11)	2-14
PSG Total Sleep Time (min.)	398.11 (71.26)	237.00-527.50
PSG Sleep Efficiency (%)	84.29 (10.33)	62.30-96.80
PSG Stage N1 (% of TST)	11.37 (7)	3.30-30.90
PSG Stage N2 (% of TST)	53.60 (6.8)	42.40-64.90
PSG Stage N3 (% of TST)	17.45 (5.5)	8.50-28.50
PSG Stage REM (% of TST)	17.74 (3.57)	10-25
Apnea-Hypopnea Index (nb/h.)	0.22 (0.34)	0-1
Arousal Index (nb/h.)	8.48 (2.8)	3.30-12.90
HF-HRV rest (ln(ms^2))	6.92(1.24)	3.82-9.03
HF-HRV worry (ln(ms^2))	6.43(1.19)	4.67-9.42
ISI Low Stress	6.64 (4.84)	0-15
ISI High Stress	7.86(5.27)	1-20
PSQI Low Stress	5.31 (2.81)	1-10
PSQI High Stress	5.86 (3.56)	0-15

ESS, Epworth Sleepiness Scale; FIRST, Ford Insomnia Response to Stress Test; ISI, Insomnia Severity Index; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; TST, total sleep time

	FIRST	*HF-HRV rest*	*HF-HRV worry*	*ISI-LS*	*ISI-HS*	*PSQI-LS*	*PSQI-HS*
FIRST	1	-.22	-.46*	.79**	.56**	.64**	.62**
HF-HRV rest		1	.83**	-.25	-.30	-.37†	-.44*
HF-HRV worry			1	-.41†	-.48*	-.43*	-.56**
ISI-LS				1	.72**	.71**	.64**
ISI-HS					1	.55**	.67**
PSQI-LS						1	.83**
PSQI-HS							1

†<.10; *< .05; ** <.01; FIRST, Ford Insomnia Response to Stress Test; HS, High Stress period; ISI, Insomnia Severity Index; LS, Low Stress period; PSQI, Pittsburgh Sleep Quality Index